TEXAS Health and Human Services

Naloxone HCl

(NARCAN® Nasal Spray)

Classification: Antidote; Opioid Antagonist

Pharmacology:
Mechanism of Action: Naloxone hydrochloride is an opioid antagonist that competes and displaces opioids at mu-opioid receptors. It reverses the effects of opioids, including respiratory depression, sedation, hypotension, and psychomimetic and dysphoric effects.
Pharmacokinetics[1]**:**
Absorption: Intranasal (43.1%) Intramuscularly (54%)

	2 mg – One Nasal Spray in one nostril 20 mg/ml (N=29)	4 mg- One Nasal Spray in one nostril 40 mg/ml (N=29)	0.4 mg intramuscular injection (N=29)
T_{max} (h) ǂ	0.33	0.50	0.38
C_{max} (ng/mL)	2.91	4.83	0.88
$T_{½}$ (h)	1.85	2.08	1.24

ǂ T_{max} reported as median

Distribution: Relatively weak plasma protein binding (albumin).
Metabolism: Naloxone hydrochloride is primarily metabolized by glucuronide conjugation in the liver.
Elimination: Following one single intranasal administration of naloxone nasal spray, mean plasma half-life was 1.85 hours for 2mg and 2.08 hours for 4 mg. After oral or intravenous dose, about 25-45% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

Indications:
Naloxone nasal spray is intended for emergency treatment of known or suspected opioid overdose presenting with respiratory and/or central nervous system depression.
Naloxone nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present.
Naloxone nasal spray is not a substitute for emergency medical care.
Limitations of Use:
Restrict prescription of naloxone nasal spray 2 mg to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

Administration:
Instruct prescription recipient to inform those around them about naloxone nasal spray and the *Instructions For Use*, emphasizing the following:

- No additional device assembly, priming, or testing required before use.
- Administer naloxone nasal spray as quickly as possible. Prolonged respiratory depression may result in central nervous system damage and death. It is important to seek emergency assistance immediately, even with use of naloxone nasal spray and continue surveilling the patient until emergency personnel arrive. Naloxone nasal spray is not a substitute for emergency medical care.
- Additional doses of naloxone nasal spray may be required until emergency medical assistance becomes available.
- Repeated sprays may be necessary for reversal of partial agonist or mixed agonist/antagonist agents (buprenorphine and pentazocine) due to longer duration of action.
- Do not attempt to reuse naloxone nasal spray. Each unit contains a single dose.
- Administer naloxone nasal spray in alternate nostrils with each dose.

Place patient in the supine position and provide support to the back of the neck, allowing the head to tilt back.

Dosage:
Initial dosing: In adults and pediatric patients, instill one spray into one nostril.
Repeat dosing: Seek emergency medical assistance after administration of first dose. Additional doses can be administered using a new naloxone nasal spray after 2 or 3 minutes if desired response is not achieved. Additional supportive and/or resuscitative measures may be helpful while waiting emergency medical assistance.

Contraindications:
Hypersensitivity to naloxone hydrochloride or any product ingredients.

Warning/Precautions**:**

- Duration of opioids may exceed naloxone nasal spray and return of respiratory and central nervous system depression may occur after initial improvement. Therefore it is necessary to contact emergency medical assistance immediately after first dose.
- Reversal of partial agonists or mixed agonist/antagonists (buprenorphine and pentazocine) may be incomplete and require larger or repeat dosing. Buprenorphine antagonism is characterized by a gradual onset of reversal effects and a decreased duration of the prolonged respiratory depression.
- Use of naloxone nasal spray in opioid dependent individuals can precipitate withdrawal symptoms (body aches, diarrhea, tachycardia, fever, runny nose, nausea or vomiting, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure).
- In opioid dependent neonates, avoid abrupt precipitation of opioid withdrawal. Use of alternative naloxone-containing products that can be dosed according to weight and titrated to effect are preferred. Neonatal withdrawal symptoms include: convulsions, excessive crying, and hyperactive reflexes.
- Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, tremulousness, tachycardia, hypertension, seizure, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events primarily occurred in patients who had pre-existing cardiovascular disorders or received other drugs that have similar adverse cardiovascular effects.
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Interactions:
Concurrent use with other opioid receptor antagonist (naldemedine, naloxegol, methylnaltrexone) may enhance the adverse/toxic effects (i.e. risk for opioid withdrawal).

Adverse Reactions:
In clinical trials, healthy adult volunteers who received 1 or 2 sprays of naloxone nasal spray reported increased blood pressure, constipation, toothache, muscle spasms, musculoskeletal pain, headache, nasal dryness, nasal edema, nasal congestion, nasal inflammation, rhinalgia, and xeroderma.

Use in Special Population:
There is limited available data on naloxone hydrochloride use in pregnant women and is insufficient to inform a drug associated risk. In animal studies, no embryotoxic or teratogenic effects have been observed. Naloxone hydrochloride can cross the placenta and precipitate withdrawal in the fetus. Careful monitoring is recommended until the mother and fetus are stabilized. Currently there is no information regarding presence of naloxone in human milk or effects on the breastfed infant or on milk production. Studies have shown that naloxone does not affect prolactin or oxytocin hormone levels.

HHSC Cost:
Narcan® Nasal Spray 4 mg/0.1 ml (2 pack): $125.00
Evzio® Auto-Injector 2 mg/0.4 ml (2 pack): $4,100
Naloxone hydrochloride 0.4 mg/1 ml vial: $6.63

Monitoring:
- Respiratory rate
- Heart rate
- Blood pressure
- Temperature
- Level of consciousness
- Oxygen saturation
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Product Identification**:**
Naloxone nasal spray 4 mg is supplied as a carton containing two blister packages each with a single spray device.

Efficacy:
Naloxone has been proven to reverse opioid overdoses and many major opioid authorities and governing bodies have released statements encouraging the practice of co-prescribing naloxone with opioid prescriptions for at risk populations. The CDC's 2016 *Guideline for Prescribing Opioids for Chronic Pain* recommends clinicians to incorporate management plan strategies to mitigate risk, such as offering naloxone, to those with increase risk of opioid overdose.[3] Increased risk factors for opioid overdose include history of overdose, history or substance use disorder, higher opioid dosages (>50 MME/day) or concurrent benzodiazepine use. After the Surgeon General's Advisory on naloxone was announced, the American Academy of Pain Medicine released a secondary statement supporting use of naloxone as an important tool in response to the opioid epidemic.[4,5] The World Health Organization in 2018 released an information sheet on opioid overdose in

support of countries promoting naloxone availability and monitoring drug trends, as well as training and management of opioid overdose.[6]
In 2016, the National Institute on Drug Abuse funded a large study to evaluate feasibility and impact of co-prescribing naloxone in patients on long-term opioid therapy. Authors found patients who received a naloxone prescription had 47% fewer opioid related ED visits per month six months after receiving naloxone and 63% fewer visits after one year (compared to those who did not receive naloxone).[7] In a follow up study, it was found that 87% of patients had successfully filled the naloxone prescription and most patients had either positive or neutral response to being offered naloxone.[8]
Smaller studies in communities have shown promising results with Opioid Overdose Education & Naloxone Distribution (OEND) programs. In Chicago, a 2006 study showed reversal (20% decrease) of a previous steadily increasing trend of heroin overdose deaths since 1991.[9] In Massachusetts, opioid overdose death rates were shown to be reduced in communities where OEND programs were implemented.[10] The study compared opioid overdose mortality rates of 19 different communities with varying implementation rates. Low implementation (1-100 people trained per 100,000 population) and high implementation (greater than 100 people trainer per 100,000 population) showed 27% and 46% reduction of opioid related mortality rates.

Conclusions:
Naloxone nasal spray is an inexpensive, effective, and accessible option to protect patients at risk for opioid overdose without the injection burden of other naloxone formulations. This formulation allows medically untrained people, close friends/family members at the emergency scene, to safely and effectively reverse overdoses without having undergone aseptic technique training and risk of being exposed to needle stick injuries. It also shows similar and comparable pharmacokinetic properties to the intramuscular formulation. The only naloxone product currently on formulary is an injectable formulation and not a suitable option for patient's discharging to the community setting. The Texas Pharmacy Association has obtained a physician signed standing order to facilitate the prescribing process of naloxone to increase accessibility for patients at risk. Naloxone nasal spray is not intended for every patient discharged on opiates. Providers should identify recipients based on risk factors outlined in the CDC Opioid Prescribing guidelines (history of overdose, substance use disorder, >50 MME/day, and/or concurrent benzodiazepine use). In conclusion, addition of naloxone nasal spray is recommended for formulary approval given current opioid guideline recommendations, supported evidence for decrease in opioid related deaths, and ideal formulation for outpatient use with similar

pharmacokinetic efficacy as naloxone injection and is less expensive than the naloxone auto-injector.

Recommendation:
Recommend for addition to formulary.

References:

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